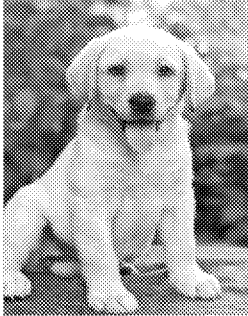




Seresto and EPA's Regulation of Pet Products



March 31, 2021

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Purpose

- The purpose of this briefing is to:
 - Present OPP's regulation of pet products.
 - Provide an update on efforts to broadly address pet risk in OPP.
 - Discuss proposals to address incidents reported on the collar Seresto.



U.S. Pet Product Regulation

- EPA regulates products applied directly to pets such as spot-ons, collars, shampoos, sprays, dips.
- In addition to typical data requirements, these products are supported by efficacy studies and a companion animal safety study.
 - The guideline for the companion animal safety study has not been updated in ~20 years and these studies are usually negative for adverse effects.
 - Small sample sizes and use of known hardy breeds detract from usefulness of these studies.
- Currently, both EPA and FDA have statutory responsibility in regulating products used on pets.
 - EPA regulates pet products applied to exterior of animals that are ***“not systemic.”***

FDA and EPA Regulation of Pet Products

- FDA regulates the majority of veterinary products in the U.S. and unlike EPA has extensive pre-market review and post-market surveillance programs under the Federal Food, Drug, and Cosmetic Act.

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	Current EPA Requirements	Current FDA Requirements
Pre-market Animal Safety Study	<u>Guideline No:</u> 870.7200 <u>Title:</u> Companion Animal Safety <u>Number of Animals:</u> 6 per sex per dose <u>Level of Concern:</u> 5X <u>Other:</u> Harmonized with previous FDA/CVM Guidance #33	<u>Guideline No:</u> 185 (VICH GL43) <u>Title:</u> Target Animal Safety for Veterinary Pharmaceutical Products <u>Number of Animals:</u> 4 per sex per dose <u>Level of Concern:</u> 5X <u>Other:</u> International harmonization
Pre-market Clinical Trials	None	<u>Guideline No:</u> 85 (VICH GL9) <u>Title:</u> Good Clinical Practice <u>Number of Animals:</u> ~200 (where 1/2 are positive control). Represents populations of actual pets rather than only test beagles. Informs labeling and contributes to the overall approval decision.
Post-market Surveillance	Aggregate summary reporting of summary numbers of adverse effects under FIFRA Section 6(a)(2). Generally only used to trigger a more detailed review.	FDA has dedicated post-marketing staff that monitor adverse reports to assure safety/effectiveness. Findings may result in changes to product, label, insert, and communication with vets and the public.

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History of EPA Mitigation of Spot ons

- In 2009, due to an increase in reports of pet incidents involving spot-on pesticide products, OPP implemented the following measures for all spot-ons:
 - 2-year time-limited conditional registrations.
 - Label mitigation to clarify instructions for safe use and provide clear indicators to prevent misuse.
 - Limitation on CSFs to one formulation.
 - Enhanced quarterly incident reporting with corresponding sales data (such as exposure scenarios and associated clinical signs).
- In 2018 OPP and 5 companies concluded a pilot using uniform templates for enhanced reporting.
 - Efforts are currently underway to request all registrants to submit their reporting in this new form.
 - As an incentive to report in the new form, EPA has agreed to remove the 2-year time-limitation registration and convert the reporting requirement from quarterly to annual.

Direct → distribution → distribution → EPA has released

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Pet Incidents Issue

- OPP currently has no standardized process for evaluating pet incidents, nor a defined precedent for when pet incidents trigger further review or potential action.
 - There are over 400 pet products registered with EPA.
 - About 40% are pet spot-on products, 10% are collars, and the rest are dips, sprays, otic (ear) applications, tags, powders, shampoos, and wipes.
 - Although ~50% of the registered pet products are collars and spot-ons, a 2018 review indicated over 90% of reported pet incidents were associated with these products.

Pet Incidents Issue

- In Registration Review, potential human health risks of concern have been identified from use on pets for several chemicals (*e.g.*, fipronil, amitraz) currently being evaluated. Regulatory actions based on pet incidents should not drive consumers toward products with potential human health risks of concern.
- In March 2019 the OPP OD was briefed on team recommendations for cross-product review of pet incident information, prompting

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Seresto Background

- The Seresto pet collar, containing imidacloprid and flumethrin, was registered in 2012 by Bayer. It is now owned by Elanco.
- The collar can be marketed for all sizes of cats and dogs for treatment against fleas, ticks, and lice.
- The collar is used on Arizona tribal lands and has successfully reduced the number of Rocky Mountain Spotted Fever infections in local tribal communities.
- We have received more than 75,000 incidents, including 1,698 pet deaths on the collar since it was registered in 2012.

Seresto Background

- Seresto is registered in the EU with label mitigation that identifies possible side effects and directs the user to remove the collar in those instances.
- In 2016, PMRA did not register Seresto d

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- The Registration Review Interim Decision for flumethrin was completed in March 2020
 - Noted the increase in pet incidents, but no label changes were required for pet safety due to limited pet incident analysis available.
- The Registration Review Interim Decision for imidacloprid is scheduled to be completed later this year.

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Adverse Event Reporting for U.S. Pesticide Incidents OPP's Incident Data System (IDS)

- FIFRA Section (6)(a)(2) requires pesticide registrants to report information concerning unreasonable adverse effects of their products to EPA.
- U.S. EPA reporting requirements are outlined in Pesticide Registration Notice (PRN) 98-3 and include:

Detailed Narrative Reports <i>ASAP – 15 days after incident</i>	<ul style="list-style-type: none">• Human Deaths
Detailed Narrative Reports <i>1 Month after incident</i>	<ul style="list-style-type: none">• Human Major/Moderate Incidents• Major Wildlife and Environmental Incidents
Aggregate Counts <i>Quarterly</i>	<ul style="list-style-type: none">• Human Minor Incidents• All Domestic Animals (i.e., death, major, moderate, minor)• Non-Major Wildlife and Environmental Incidents

Source: [PRN 98-3: Guidance on Final FIFRA 6\(a\)\(2\) Regulations for Pesticide Product Registrants](#)

Adverse Event Reporting for U.S. Pesticide Incidents OPP's Incident Data System (IDS)






Pet Incident Data Challenges/Limitations

- Aggregate reporting of pet incidents lacks narrative information on individual incidents
 - Pet information, including species, sex, age, health status
 - Nature of Exposure
 - Clinical Signs
- Similar to drugs monitored by FDA, adverse event reports alone are not an indicator of the safety profile of pet products
 - Based on observation of consumers/clinical professionals and not verified
 - Reported adverse effects may be unrelated to product use
 - Rate of adverse incidents cannot be determined with additional information (i.e., use rates)
 - Subject to reporting bias (robustness of company monitoring program, consumer awareness, location of toll-free numbers on product labels, etc.)

OPP Evaluation Approach for Pet Incident Reports

What incident data is collected by OPP?

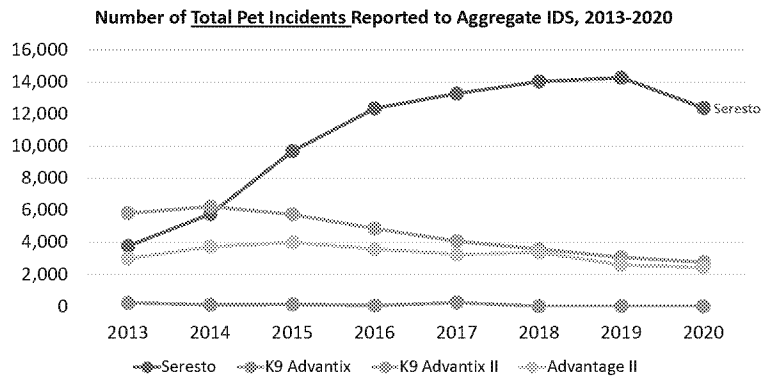
What information could strengthen OPP's reviews of pet incidents?

Tier	Data Source	Description
 Level 0: Aggregate Incident Data System Query	 OPP's Incident Data System	<ul style="list-style-type: none"> Descriptive analysis using OPP's Incident Data System (IDS). IDS captures data on domestic animal (pet) incidents received under FIFRA 6(a)(2) from registrants in aggregate form on a quarterly basis.
 Level 1: Reporting Odds Ratio (RON)	OPP's Incident Data System	<ul style="list-style-type: none"> Comparison of disproportionality of adverse outcomes (typically death and major) across pet products of interest. Can be estimated with existing data but may be biased due to differential reporting across products (e.g., Under-Reporting, Some Data Reporting, Weber Effect).
 Level 2: Incident Rate Ratio (IRR)	OPP's Incident Data System Enhanced Reporting Data on Death, Sales	<ul style="list-style-type: none"> Comparison of the rate of a given outcome (typically death and major) for one product to the rate of [same] outcome to another. Estimation of rates requires sponsor to submit sales data.
 Level 3: Signal-Based Case-by-Case Review & Causality Analysis	Enhanced Reporting Data on Death, Sales Information	<ul style="list-style-type: none"> Signal-based case-by-case review evaluated cases on an individual basis and incorporates information in the submitter narrative. This may involve investigating if it for clinical signs and incorporate causality analysis.

OPPS → OPP's Incident Data System → OPP's Incident Data System

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OPP Analysis of Seresto and Select Bayer Pet Products (IDS, 2013-2020)



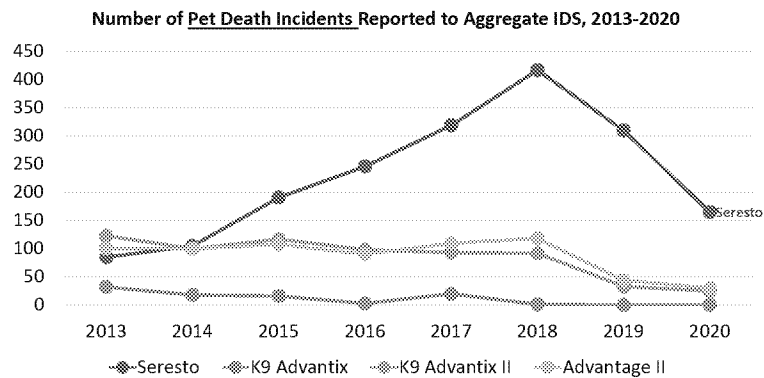
- From 2013-2018, **270% increase** is total number of reported incidents to IDS
- From 2018-2020, **flattening/decrease** in reported incidents.*

**However, unclear if this is due to reporting changes by company.*

Source: IDS Inc. (2013-2020) - Data provided by IDS Inc. (2013-2020)

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OPP Analysis of Seresto and Select Bayer Pet Products (IDS, 2013-2020)



- From 2013-2018, **390% increase** is total number of deaths reported to IDS
- From 2018-2020, **decrease** in reported death incidents.*

**However, unclear if this is due to reporting changes by company.*

Source: IDS, 2013-2020

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Considerations

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Status of OPP Review of Seresto Pet Incidents

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Status of OPP Review of Seresto Pet Incidents

- **Bayer Presentation to EPA (July 2019 Meeting)**

- Company representatives presented analysis of incidents trends that accounted for Seresto market share. Company suggested:
 - Incident reporting has decreased as U.S. market share has increased.
 - Seresto incidents trend is normalizing and is now on par with the safety profile of K9 Advantix.
- While Bayer shared some summary information during the meeting, the company has not formally submitted the underlying data and supporting documentation. As such, OPP has been unable to replicate their findings and examine further.

Status of OPP Review of Seresto Pet Incidents

- **Data Limitations and Needs**

- OPP can continue to perform descriptive analysis of trends
- However, sales data and narrative information needed to fully assess incident trends and link use with severe outcomes and death.
 - Updated comparison of incident rates relative to product market share
 - Narrative review of clinical symptoms and causality assessment
- Information requested in Excel-reporting template (2016) for spot-on products pilot would allow comparative product analysis of Seresto and related pet products.

Current Seresto Issue

- We continue to receive reports of pet incidents.
 - In 2019, 384 pet deaths were recorded.
 - Neurological signs and seizures anecdotally appear to be related to the collar's use
- In March 2021, USA Today published an article after receiving an aggregate incident report via FOIA.
 - As of 3/17 there have been 2 Congressional inquiries on the incidents since the article published.
 - 75,000 incidents, 1698 pet deaths, and nearly 1000 human incidents over 8 years.
 - Preliminary analysis of 2020 data adds another 11,000 total incidents.
- **We need sales data and additional incident details to give context to the incident numbers.**



Recommended Next Steps—Short Term

Ex. 5 Deliberative Process (DP)

Direct --> Deliberative --> Deliberative --> Deliberative

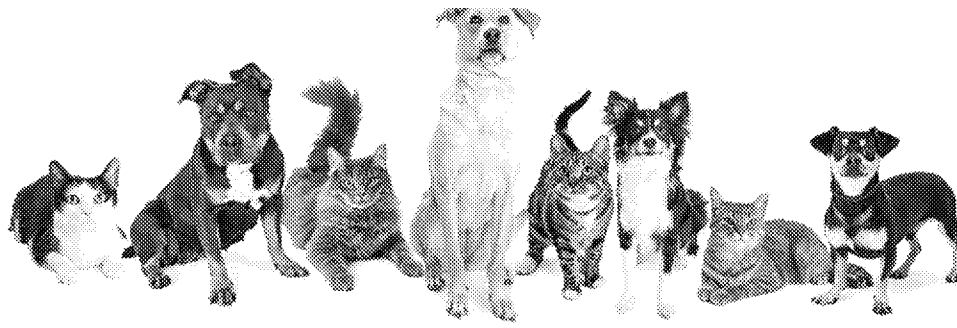
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Recommended Next Steps—Medium Term

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Recommended Next Steps—Long Term

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Thank You! Questions?

6. ADVERSE REACTIONS

In rare cases behavioural disorders that may include hiding, vocalization, hyperactivity, excessive licking and/or grooming or scratching at the application site may be observed in animals that are not used to wearing collars on the first few days after fitting. Aggression after collar application was reported in very rare cases. Ensure that the collar is fitted correctly.

Application site reactions such as pruritus, erythema and hair loss may occur. These have been reported as rare and usually resolve within 1 to 2 weeks. In single cases, a temporary collar removal may be recommended until the symptoms have disappeared.

In very rare cases, application site reactions such as dermatitis, inflammation, eczema, lesions or haemorrhage may occur and in these instances, collar removal is recommended.

In rare cases neurological symptoms as ataxia, convulsions and tremor may occur. In these cases collar removal is recommended.

Also in rare cases in dogs, slight and transient reactions as depression, change of food intake, salivation, vomiting and diarrhea might occur initially.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports)

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

Congressional Inquiries

1. Raja Krishnamoorthi – Chairman – Subcommittee on Economic and Consumer Policy – due 3/30/21

- A description of IDS.
- A list of all pet products in IDS with pet death/injury or human death/injury.
- Policies and procedures regarding various aspects of IDS.

2. Bernard Sanders, VT

- Requests response to constituent letter.
 - Letter demands EPA to immediately issue a stop sale.

EPA's Regulatory Options under FIFRA

1. Suspension under Section 6

- A Notice of Intent to Cancel (NOIC) must be issued at the same time as a suspension order unless EPA determines an emergency exists.
 - In the case of emergency the NOIC must be issued no later than 90 days after the emergency suspension order.
- To issue an NOIC, EPA must determine that the product as registered does not appear to meet the FIFRA standard.
- Both a suspension order and NOIC afford the registrant the right to request a hearing.

2. Enforcement under Section 13a

- A Stop Sale, Use, or Removal Order (SSURO) when EPA has reason to believe on the basis of inspections or tests that the product is in violation of FIFRA.
- EPA has no authority to require product recall but registrants may volunteer to recall products.

10/2018 - 10/1/2019 - 10/1/2019 - 10/1/2019

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